(19) Europäisches Patentamt
European Patent Offic
Office européen des brevets

(11) Publication number: **0 251 459**
A2

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: **87304189.1**

(51) Int. Cl.⁴: **A61K 9/22**

(22) Date of filing: **12.05.87**

Claim for the following Contracting State: AT.

(30) Priority: **05.06.86 GB 8613688**

(43) Date of publication of application:
07.01.88 Bulletin 88/01

(84) Designated Contracting States:
DE FR GB IT

(71) Applicant: **Euroceltique SA**
122 Boulevard de la Petrusse
Luxembourg(LU)

(72) Inventor: **Elger, Gordon Anthony**
99 Greenfields Earith
Huntingdon Cambridge(GB)
Inventor: **Leslie, Stewart Thomas**
4 Babraham Road
Cambridge(GB)
Inventor: **Malkowska, Sadra Therese Antoinette**
14 Abrahams Close
Landbeach Cambridge(GB)
Inventor: **Miller, Ronald Brown**
Bruderholzallee, 191
CH-4059 Basel(CH)
Inventor: **Neale, Philip John**
28 London Road
Harston Cambridge(GB)

(74) Representative: **James, Stephen Richard, Dr.**
Napp Research Centre Cambridge Science Park Milton Road
Cambridge CB2 2RA(GB)

(54) **Controlled release pharmaceutical composition.**

(57) A solid, controlled release, pharmaceutical composition comprising an active ingredient incorporated in a matrix comprising a first substance selected from a water soluble polydextrose and a water soluble cyclodextrin and a second substance selected from a C_{12}-C_{36} fatty alcohol and a polyalkylene gylcol.

Preferably the first substance is a cyclodextrin, especially a beta-cyclodextrin, whilst the second substance is a C_{14}-C_{22} fatty alcohol, especially stearyl alcohol, cetyl alcohol, cetostearyl alcohol or myristyl alcohol. The matrix may also contain a cellulose ether, especially a hydroxyalkylcellulose or a carboxyalkylcellulose.

EP 0 251 459 A2

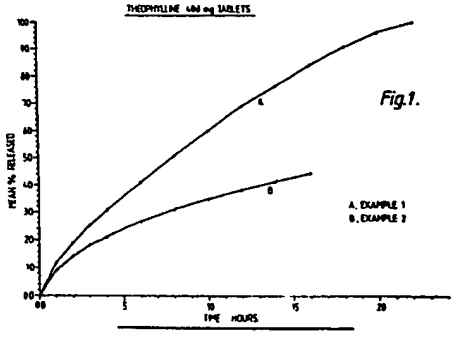

Fig.1.

CONTROLLED RELEASE PHARMACEUTICAL COMPOSITION

The present invention relates to a solid controlled release pharmaceutical composition.

A "controlled release pharmaceutical composition" is one that achieves slow releases of a drug over an extended period of time and extends the duration of drug action over that achieved by conventional delivery. Preferably such a composition maintains drug level in the blood or target tissue within the therapeutic range for 8 hours or more.

A controlled (sustained) release pharmaceutical composition containing an active ingredient has many advantages over a normal release form of the same ingredient. These include a reduction of the frequency of administration, a decrease in side effects and the maintenance of effective concentrations of the active material in the blood.

It is an object of the present invention to provide a controlled release pharmaceutical composition that exercises particularly good control over the release of the active ingredient.

Other objects and advantages of the present invention will become apparent from the following detailed description thereof.

According to the present invention, therefore, there is provided a solid, controlled release, pharmaceutical composition comprising an active ingredient incorporated in a matrix comprising a first substance selected from a water-soluble polydextrose and a water-soluble cyclodextrin and a second substance selected from a C_{12}-C_{36} fatty alcohol and a polyalkylenen glycol.

In the present specification, "water soluble" means that the polydextrose or cyclodextrin dissolves to a level of at least 1% (w/w) in water at 25°C.

Although the polydextrose employed in the present composition may have an average molecular weight of between about 360 and 10^6, preferably the polydextrose has a number average molecular weight between 1000 and 12000. Polydextrose is a non-nutritive polysaccharide, prepared by the condensation polymerisation of saccharides in the presence of polycarboxylic acid catalysts, under reduced pressure.

Polydextrose is described in US Patents No. 3766105 and 3786794 (the contents of which documents are incorporated herein by reference) and is available from Pfizer Inc., New York. Commercially available polydextrose polymer is generally a low molecular weight, water-soluble, randomly bonded polymer of glucose containing minor amounts of sorbitol end groups and citric acid residues attached to the polymer by mono-and di-ester bonds. The number average molecular weight of this commercially available material is 1500, ranging from about 360 to about 20,000.

In the present specification, "cyclodextrin" incorporates both the naturally occurring clathrates obtained from the action of Bacillus macerans amylase on starch to form homogeneous cyclic alpha (1-4) linked D-glucopyranose units (ie. alpha, beta-and gamma-cyclodextrin) but also the methylated derivatives of these natural products, especially of beta-cyclodextrin (eg. heptakis (2,6-di-O-methyl)-beta-cyclodextrin and heptakis (2,3,6-tri-O-methyl)-beta-cyclodextrin.

In a preferred embodiment of the present composition the cyclodextrin (or methylated derivative) is a beta-cyclodextrin.

The amount of polydextrose and/or cyclodextrin present in the composition of this invention will be determined by a number of factors, including the active ingredient to be administered and the rate of drug release required. Preferably, however, the compositions will contain between 1% and 80% (w/w), especially between 1% and 50% (w/w) of polydextrose and/or cyclodextrin, most especially between 2% and 40% (w/w) of polydextrose and/or cyclodextrin.

The C_{12}-C_{36} fatty alcohol may be any digestible, long chain alcohol. Preferably, it has a melting point between 25° and 95°C. In a particularly preferred embodiment of this invention, the alcohol is a C_{14}-C_{22} fatty alcohol such as stearyl alcohol, myristyl alcohol, cetyl alcohol and, which is preferred, cetostearyl alcohol.

The polyalkylene glycol may be, for example, polypropylene gylcol or, which is preferred, polyethylene glycol. In a particularly preferred embodiment of the present invention the second substance in the controlled release matrix is a C_{12}-C_{36} fatty alcohol, especially a C_{14}-C_{22} fatty alcohol.

In addition to the polydextrose, cyclodextrin and alcohol/glycol, the present composition may also include further ingredients which can contribute to the control of the active ingredient's release and are compatible with polydextrose, cyclodextrin, fatty alcohol and polyalkylen glycol.

Of thes polymers, the cellulose ethers, especially hydroxyalkylcellulos s and carboxyalkylcelluloses, most especially hydroxethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose and sodium carboxymethyl cellulose, ar preferred.

In pref rred compositions according to this invention the ratio of polydextrose/cyclodextrin/hydrophilic and/or hydrophobic polymer to fatty alcohol/glycol is betw en 6 to 1 and 1 to 6, especially between 4 to 1 and 1 to 4.

Wh n the polydextrose and/or cyclodextrin is combined with the C_{12}-C_{36} fatty alchol and/or polyalkylene glycol, the matrix itself is novel. Thus, in another aspect of the present invention, there is provided a preparation for use in the production of a solid, controlled release pharmaceutical composition comprising a matrix of a first substance selected from a water-soluble polydextrose and a water-soluble cyclodextrin and a second substance selected from a C_{12}-C_{36}, especially C_{14}-C_{22}, fatty alcohol and a polyalkylene glycol. Optionally the matrix may also contain at least one of a hydroxyalkyl cellulose and a carboxyalkyl cellulose. Preferably the ratio of polydextrose/cyclodextrin/ cellulose to fatty alcohol/glycol is between 6 to 1 and 1 to 6, especially between 4 to 1 and 1 to 4.

In addition to the above materials, the present controlled release composition may also contain excipients, such as binders, disintegrating agents, colours, flavours, preservatives, stabilisers, glidants and lubricants, the use of which will be well known to those skilled in the pharmaceutical art.

Although the present controlled release composition may be in any solid dosage form, for example, a suppository or a pessary, it is preferably adapted for oral administration. In the present specification "oral administration" incorporates buccal and sublingual administration. Thus, the preferred oral dosage forms include tablets, buccal tablets, sublingual tablets, lozenges, capsules containing, for example, granules or pellets, and dragees.

Any active ingredient that may be administered by the oral, buccal, sublingual, rectal or vaginal routes may be employed in the controlled release composition of this invention. Thos medicaments having a biological half-life below about 8 hours, however, are particularly suitable for incorporation in the present composition.

Examples of active ingredients that may advantageously be incorporated in the present composition are,

1) Anti-allergic drugs, such as cyclizine, dimethindene maleate and triprolidine hydrochloride,

2) Anti-diabetic drugs, such as chlorpropamide, glibenclamide, metformin and tolbutamide,

3) Hormones,

4) Antiarrhythmic agents, such as disopyramide, procainamide, propranolol and quinidine,

5) Anti-inflammatory agents, such as aspirin, diclofenac sodium flurbiprofen, ibuprofen, indomethacin, ketoprofen, naproxen and phenylbutazone,

6) Antiemetic drugs, such as metoclopramide,

7) Diuretics, such as amiloride, bendrofluazide, bumetanide, cyclopenthiazide, ethacrynic acid, frusemide, hydrochlorothiazide, triampterene, chlorthalidone and spironolactone,

8) Anti-anginal agents, such as nitrogylcerin, isosorbide dinitrate pentaerythritol tetranitrate, verapamil and diltiazem.

9) Vasodilators, such as nifedipine, naftidrofuryl oxalate, and nicardipine,

10) Antihypertensive agents, such as clonidine, indoramin, guanethidine, methyldopa, oxprenolol, captopril, hydralazine and propranolol,

11) Bronchodilators, such as salbutamol, isoprenaline and terbutaline,

12) CNS stimulants, such as caffeine and amphetamine,

13) Anti-histamines, such as clemastine fumarate, mepyramine, chlorpheniramine, brompheniramine, diphenhydramine.

14) Analgesic agents, such as morphine, codeine, phenazocine, dihydrocodeine, hydromorphone, meptazinol, phenacetin, pethidine, paracetamol, oxycodone, diamorphine, nalbuphine, buprenorphine, and mefenamic acid,

15) Vitamins, such as Vitamin B1, Vitamin B2, Vitamin B6, Vitamin C and Vitamin E,

16) Antidepressants, such as lofepramine, amitriptyline, doxepin, maprotiline, imipramine, desipramine and mianserin,

17) Tranquilisers, such as chlordiazepoxide and diazepam,

18) Hematinic agents, such as ferrous fumarate,

19) Respiratory stimulants, such as nikethamide,

20) Antibacterial agents, such as polymyxin, streptomycin, sulphonamides, penicillins, erythromycin, cephalosporins, nalidixic acid, tetracyclines, hexamine salts, gentamicin and nitrofurantoin,

21) Hypnotic agents such as barbiturates, dichloral phenazone, nitrazepam and temazepam,

22) Antiviral agents, such as idoxuridine,

23) Vasoconstrictors, such as angiotens in amide, dihydroergotamine, and ergotamine,

24) Topical anaesthetics, such as benzocaine,

25) Anticholinergic agents, such as scopolamine, atropine and propantheline,
26) Adrenergic drugs, such as phenylephrin hydrochloride, phenylpropanolamin hydrochloride and pseudoephedrine,
27) Anthelmintic agents, such as diethylcarbamazine,
28) Corticosteroids, such as dexamethasone, prednisone, prednisolone and triamcinolone acetonide,
29) Inorganic drugs, such as lithium carbonate, potassium chloride and lithium sulphate,
30) Antacids, such as aluminium trisilicate and aluminium hydroxide,
31) Antiulcer agents, such as cimetidine and ranitidine,
32) Cofactors, such as nicotinic acid,
33) Antipsychotic agents, such as thioridazine, trifluoperazine, fluphenazine and haloperidol,
34) Laxatives, such as bisacodyl and magnesium hydroxide,
35) Antiperistaltic agents, such as diphenoxylate,
36) Anticoagulant agents, such as warfarin,
37) Haemostatic agents, such as epsilon-aminocaproic acid,
38) Antinauseant agents, such as metoclopramide, pyridoxine and prochlorperazine,
39) Anticonvulsant agents, such as sodium valproate and phenytoin sodium,
40) Neuromuscular drugs, such as dantrolene sodium,
41) Hypoglycaemic agents, such as chlorpropramide, glucagon and tolbutamide,
42) Thyroid drugs, such as thyroxine, triiodothyronine and propylthiouracil,
43) Uterine relaxant, such as ritodrine,
44) Appetite suppressants, such as phentermine, diethylpropion HCl and fenfluramine HCl,
45) Erythropoietic substances, such as folic acid, calcium gluconate, and ferrous sulphate,
46) Expectorants, such as carbocisteine and, guiaphenesin,
47) Cough suppressants, such as noscapine, dextromethorphan and oxycodone,
48) Antiuricemic drugs, such as allopurinol, probenecid and sulphinpyrazone,

Preferably the active ingredient is a water-insoluble drug. In the present specification, a water insoluble drug is a drug that dissolves in water (pH 5) at 20°C to a concentration of less than 1.0mgml^{-1}, preferably less than 0.5mgml^{-1}.

According to another feature of the present invention, the solid, controlled release, pharmaceutical composition is prepared by mixing an active ingredient with a first substance selected from a water soluble polydextrose and a water soluble cyclodextrin and a second substance selected from a C_{12}-C_{36} fatty alcohol and a polyalkylene glycol, optionally in the presence of one or more of the following excipients, a hydrophilic or hydrophobic polymer, a binder, a disintegrating agent, a colour, a flavour, a preservative, a stabiliser, a glidant and a lubricant. Preferably the alcohol is a C_{14}-C_{22} fatty alcohol.

In a particularly preferred embodiment of this feature of the invention a solid, controlled release, pharmaceutical composition, in unit dosage form and for oral administration (as hereinbefore defined), is prepared by granulating an active ingredient with a first substance selected from a water soluble polydextrose and a water soluble cyclodextrin and, optionally, mixing with one or more of the following excipients, a hydrophilic or hydrophobic polymer (other than polydextrose), a binder, a disintegrating agent, a colour, a flavour, a preservative, a stabiliser, a glidant or a lubricant, to form granules, mixing the granules formed with a second substance selected from a C_{12}-C_{36} fatty alcohol and a polyalkylene glycol and compressing the granules to give an oral, solid unit dosage form containing a predetermined, therapeutically active, quantity of the active ingredient. Preferably the alcohol is a C_{14}-C_{22} fatty alcohol.

Depending on the particular case, the method of preparation of the granules may involve for example wet granulation or direct compression.

Once the oral, solid unit dosage form has been prepared it may, if desired, be coated, for example with a gastro-resistant coating.

In a further, particularly preferred embodiment of this feature of the invention a solid, controlled release, pharmaceutical composition in the form of a capsule is prepared by pelletising, spheronising or granulating an active ingredient with a first substance selected from a water soluble polydextrose and a water soluble cyclodextrin and a second substance selected from a C_{12}-C_{36}, especially C_{14}-C_{22}, fatty alcohol and polyalkylene gylcol and, optionally, one or more of the optional ingredients employed in the preparation of the oral, unit dosage form above, to form pellets, spheroids or granules and encapsulating the pellets, spheroids or granules to give a capsule containing a predetermin d, th rapeutically active, quantity of the active ingredient.

Prior to filling the capsule with the pellets, th spheroids or the granules, the pellets/spheroids/granules may be coat d, for example with a gastro-resistance coating.

According to another feature of the present invention, there is provided a proc ss for the preparation of a matrix for admixtur with an active ingredient to form a controlled release pharmaceutical composition comprising mixing a first substance selected from a water soluble polydextrose and a water soluble cyclodextrin with a second substance selected from a C_{12}-C_{36} especially a C_{14}-C_{22}, fatty alcohol and a polyalkylene glycol, especially glycol to form a controlled release matrix

Once the matrix has been granulated it can then be mixed with a predetermined amount of the active ingredient and, optionally compressed, to give a controlled release pharmaceutical composition according to the invention.

Predetermined release patterns of unusually reliable and constant characteristics can be secured using the present composition. This is often very important medically, especially when treating patients having coronary diseases, such as angina pectoris, or related problems, such as circulatory disorders or abnormal blood pressure, or when treating psychotropic disorders, such as manic depression or schizophrenia or when treating bronchial disorders or moderate to severe pain. The present composition may also be extremely useful in the treatment of ulcerated tissues or mucous lesions and other conditions which arise from local hyperacidity or metabolic dysfunction in the physiological system. The present composition is therefore extremely versatile and adaptable giving a wide range of application and end use.

The present solid, controlled release, pharmaceutical composition, together with methods for its preparation will now be described by way of example only, with particular reference to the Figures in which,

Figure 1 compares the release rates of two theophylline controlled release formulations, one containing hydroxyethylcellulose and cetostearyl alcohol, the other polydextrose and cetostearyl alcohol,

Figure 2 compares the release rates of two pyridoxine hydrochloride controlled release formulations, one containing hydroxyethylcellulose and cetostearyl alcohol, the other polydextrose and cetostearyl alcohol, and

Figure 3 compares the release reates of two metoclopramide hydrochloride controlled release formulations, one containing hydroxyethylcellulose and cetostearyl alcohol, the other polydextrose and cetostearyl alcohol.

Example 1 (Comparative)

Anhydrous theophylline (40gm) was wet granulated with hydroxyethylcellulose (2.5gm; Natrosol 250HX, Trade Mark) and the granules were sieved through a 16 mesh screen. The granules were then dried in a FBD at 60°C.

To the warmed theophylline containing granules was added a molten mixture of polyethylene glycol PEG 6000 (5.0gm) and cetostearyl alcohol (4.0gm). This mixture was allowed to air cool and then passed through a 16 mesh screen.

Talc (1.0gm) and magnesium stearate (1.0gm) were then mixed with the granules. The granules were compressed to give 100 tablets each containing.

	mg/tablet
Theophylline anhydrous	400
Hydroxyethylcellulose	25
PEG 6000	50
Cetostearyl alcohol	40
Talc	10
Magnesium stearate	10

Example 2

The procedure of Example 1 was followed except that polydextrose replaced the hydroxyethylcellulose. This gave 100 tablets, each containing

	mg/tablet
Theophylline anhydrous	400
Polydextrose	25
PEG 6000	50
Cetostearyl alcohol	40
Talc	10
Magnesium stearate	10

A comparison of the release rates of theophylline from tablets prepared as described in Examples 1 and 2 is shown in Figure 1. The dissolution rates were measured by the USP Paddle Method at 100 rpm in 900 ml of aqueous buffer (pH 6.5).

Example 3 (Comparative)

Pyridoxine hydrochloride (10gm) and hydrogenated castor oil (1.5gm) were granulated with hydroxyethylcellulose (2.0gm, Natrosol 250HX) and the granules were sieved through a 16 mesh screen and dried in a FBD at 60°C.

To the pyridoxine hydrochloride containing granules, molten cetostearyl alcohol (3.5gm) was added. This mixture was allowed to air cool and then passed through a 16 mesh screen.

Talc (0.3gm) and magnesium stearate (0.1gm) were mixed with the granules. This mixture was compressed to give 100 tablets each containing,

	mg/tablet
Pyridoxine HCl	100
Hydroxyethylcellulose	20
Hydrogenated castor oil	15
Cetostearyl alcohol	35
Talc	3
Magnesium stearate	1

Example 4

The procedure of Exampl 3 was followed except that polyd xtrose replaced the hydroxyethylcellulose. This gave 1OO tablets each containing,

	mg/tablet
Pyridoxine HCl	100
Polydextrose	20
Hydrogenated castor oil	15
Cetostearyl alcohol	35
Talc	3
Magnesium stearate	1

A comparison of the release rates of pyridoxine HCl from tablets prepared as described in Examples 3 and 4 is shown in Figure 2. The dissolution rates were measured by the USP Paddle Method at 1OO rpm in 9OO ml of aqueous buffer (pH 6.5).

Example 5 (Comparative)

Metoclopramide HCl (3gm) was wet granulated with anhydrous lactose (17gm) and hydroxyethylcellulose (2gm; Natrosol 25OHX) and the granules were seived through a 16 mesh screen. The granules were then dried in an FBD at 6O°C.

To the warmed metoclopramide containing granules was added molten cetostearyl alcohol (7gm). The mixture was allowed to air cool and then passed through a 16 mesh screen.

Talc (O.6gm) and magnesium stearate (O.4gm) were mixed with the granules. The granules were then compressed to give 1OO tablets each containing,

	mg/tablet
Metoclopramide HCl	30
Anhydrous lactose	170
Hydroxyethylcellulose	20
Cetostearyl alcohol	70
Talc	6
Magnesium stearate	4

Exampl 6

Anhydrous lactose (17gm) and polydextros (2gm) w re dry mix d. Molten c tostearyl alcohol (7gm) was added to the dry mixed powders. The mixture was allowed to cool and then passed through a 16 mesh screen.

Metoclopramide HCl (3gm), talc (6gm) and magnesium stearate (4gm) were then mixed with the polydextrose/wax granules and compressed to give 100 tablets each containing,

	mg/tablet
Metoclopramide HCl	30
Anhydrous lactose	170
Polydextrose	20
Cetostearyl alcohol	70
Talc	6
Magnesium stearate	4

A comparison of the release rates of metoclopramide HCl from tablets prepared as described in Examples 5 and 6 is shown in Figure 3. The dissolution rates were measured by the USP Paddle Method at 100 rpm in 900 ml of aqueous buffer (pH 6.5).

Example 7

Anhydrous theophylline (40gm) was wet granulated with polydextrose (21.8gm) and the granules were sieved through a 16 mesh screen. The granules were dried in a FBD at 60°C.

To the warmed theophylline containing granules was added a molten mixture of polyethylene glycol 6000 (2.9gm), polyethylene glycol 1000 (1.45gm) and cetostearyl alcohol (2.9gm). This mixture was allowed to air cool and then passed through a 16 mesh screen.

Talc (1.0gm) and magnesium stearate (0.45gm) were then mixed with the granules. The granules wer compressed to give 100 tablets each containing,

	mg/tablet
Theophylline anhydrous	400
Polydextrose	218
PEG 6000	29
PEG 1000	14.5
Cetostearyl alcohol	29
Talc	10
Magnesium stearate	4.5

The dissolution rate in-vitro of those tablets were measured by the USP Paddle Method at 100rpm in 900ml of aqueous buffer (pH 6.5). Results are shown in Table 1.

TABLE 1

In vitro Dissolution of Theophylline Tablets

Time (Hours)	% (by wt) Released
2	21.7
4	33.7
6	42.3
8	49.0
10	54.3
12	58.3
14	62.0
16	65.0
18	67.8

Example 8

Naproxen (50gm), dicalcium phosphate (16.4g), lactose (2.5gm), polydextrose (2.0gm) and hydroxypropylmethylcellulose (2.0gm) were wet granulated and granules were sieved through a 16 mesh screen. The granules were then dried in a FBD at 50°C. Talc (1.35gm) and magnesium stearate (0.75gm) were then added and mixed with the granules. The granules were then compressed to give 100 tablets containing;

	mg/tablet
Naproxen	500
Dicalcium phosphate, anhydrous	164
Lactose monohydrate	25
Polydextrose	20
Hydroxypropylmethylcellulose	20
Talc	13.5
Magnesium stearate	7.5

The dissolution rate in-vitro of these tablets was measur d by th USP Paddle Method at 100rpm in 900ml of aqueous buffer (pH 7.2). Results are shown in Tabl 2.

TABLE 2

In vitro Dissolution of Naproxen Tablets

Time (Hours)	% (by wt) Released
1	22.3
2	49.9
3	74.4
4	91.1
5	95.9

Example 9

Naproxen (50gm), lactose (11.25gm), polydextrose (0.75gm) and povidone (2.0gm) were wet granulated and the granules were sieved through a 16 mesh screen. The granules were dried in a FBD at 60°C. Talc (1.2gm) and magnesium stearate (0.6gm) were mixed with the granules. The granules were compressed to give 100 tablets cores each containing;

	mg/tablet
Naproxen	500
Lactose monohydrate	112.5
Polydextrose	7.5
Povidone	20
Talc	12
Magnesium stearate	6

The tablet cores were then coated with an aqueous formulation (100ml) containing polyvinylacetate phthalate (15gm) and 0.88 ammonia solution (0.18ml) until the cores were coated with about 20mg (dry weight) of coat.

The in-vitro dissolution rate of these tablets was measured by placing the tablets in 0.1N hydrochloric acid for 2 hours and thereafter continuing the USP Paddle Method at 100rpm in 900ml of aqueous buffer pH 7.2. Results are shown in Table 3.

TABLE 3

In vitro Dissolution of Naproxen Tablets

Time (Hours)	Medium	% (by wt) Released
1	0.1N Hydrochloric Acid	0
2	0.1N Hydrochloric Acid	0
3	pH 7.2 Buffer	12.5
4	pH 7.2 Buffer	28.3
5	pH 7.2 Buffer	43.4
6	pH 7.2 Buffer	60.3
7	pH 7.2 Buffer	71.9
8	pH 7.2 Buffer	78.6
10	pH 7.2 Buffer	85.3
12	pH 7.2 Buffer	88.1
14	pH 7.2 Buffer	92.1

Example 10

A complex of indomethacin and beta-cyclodextrin was prepared as described in GB 2016499A, Example 1.

The indomethacin complex (360gm), lactose (20gm) and dicalcium phosphate (62gm) were wet granulated and the granules were sieved through a 16 mesh screen. The granules were then dried in a FBD at 60°C.

To the warmed indomethacin containing granules was added molten cetostearyl alcohol (80gm). This mixture was allowed to air cool and then passed through a 16 mesh screen. Talc (2.0gm) and magnesium stearate (1.0gm) were then mixed with the granules. The granules were then compressed to give 100 tablets each containing:

	mg/tablet
Indomethacin complex	360.0 (equivalent to 50mg indomethacin)
Lactose, anhydrous	20.0
Dicalcium phosphate	62.0
Cetostearyl alcohol	80.0
Talc	2.0
Magnesium stearate	1.0

Examples 11-13

Examples 2, 4 and 6 were repeated except that heptakis (2,6-di-O-m thyl)-beta-cyclodextrin replaced polydextrose.

Examples 14-16

Examples 7, 8 and 9 were repeated except that beta-cyclodextrin replaced polydextrose.

Example 17

Polydextrose (28gm) was mixed with a mixture of molten cetostearyl alcohol (6gm) and polyethylen glycol 4000 (6gm). The granules were allowed to cool and sieved through a 20 mesh screen.

Theophylline (40gm) was granulated with a solution of povidone (1.2gm) in water. The granules w re sieved through a 12 mesh screen and dried in a fluid bed drier. The granules were then sieved through a 20 mesh screen.

The theophylline granules and the polydextrose/wax granules were dry mixed with purified talc (0.6gm). Prior to compression, magnesium stearate (0.6gm) and purified talc (0.6gm) were mixed with the granules. This mixture was then compressed to give 100 tablets each containing,

	mg/Tablet
Theophylline	400
Povidone	12
Polydextrose	280
Cetostearyl Alcohol	60
Polyethylene Glycol 4000	60
Purified Talc	12
Magnesium Stearate	6

The in-vitrodissolution rate of these tablets was measured by the USP Paddle Method at 100rpm in 900ml of aqueous buffer (pH 6.5). Results are shown in TABLE 4.

TABLE 4

In Vitro Dissolution of Theophylline Tablets

Time (Hours)	% (by wt) Released
1	10.3
2	15.3
4	22.8
8	33.9
12	42.3
16	48.4
24	61.4

Example 18

The procedure of Example 17 was followed except that the amounts used were chosen such that each tablet contained,

	mg/tablet
Theophylline	400
Povidone	12
Polydextrose	140
Cetostearyl Alcohol	30
Polyethylene Glycol 4000	30
Purified Talc	9
Magnesium Stearate	4.5

The in-vitrodissolution rate of these tablets was measured as described in Example 17. Results are given in TABLE 5.

TABLE 5

In Vitro Dissolution of Theophylline Tablets

Time (Hours)	% (by wt) Released
1	10.9
2	16.4
4	24.5
8	35.6
12	45.5
16	54.5
24	72.2

Example 19

The procedure of Example 17 was followed except that the amounts used were chosen such that each tablet contained,

	mg/Tablet
Theophylline	400
Povidone	12
Polydextrose	93.3
Cetostearyl Alcohol	20
Polyethylene Glycol 4000	20
Purified Talc	8
Magnesium Stearate	4

The in-vitrodissolution rate of these tablets was measured as described in Example 17. Results are given in TABLE 6.

TABLE 6

In Vitro Dissolution of Theophylline Tablets

Time (Hours)	% (by wt) Released
1	12.4
2	19.2
4	29.5
8	44.8
12	56.5
16	68.6
24	91.9

Example 20

The procedure of Example 17 was followed except that the amounts used were chosen such that each tablet contained,

	mg/Tablet
Theophylline	400
Povidone	12
Polydextrose	70
Cetostearyl Alcohol	15
Polyethylene Glycol 4000	15
Purified Talc	7.8
Magnesium Stearate	3.7

The in-vitro dissolution rate of these tablets was measured as described in Example 17. Results are given in TABLE 7.

TABLE 7

In Vitro Dissolution of Theophylline Tablets

Time (Hours)	% (by wt) Released
1	12.7
2	19.6
4	30.9
8	48.6
12	66.5
16	80.8
24	94.5

Example 21

Theophylline (40gm) and polydextrose (21.8gm) were mixed and granulated with water. The granules were dried in a fluid bed drier. The dried granules were sieved through a 16 mesh screen. The dried granules were mixed with a molten (70°C) mixture of PEG 6000 (2.9gm) and lauryl alcohol (2.9gm). The "waxed" granules were then cooled, before blending with talc (1.0gm) and magnesium stearate (0.4gm). Compression of the granules gave 100 tablets each containing,

	mg/Tablet
Theophylline	400
Polydextrose	218
Polyethylene Glycol 6000	29
Lauryl Alcohol	29
Purified Talc	10
Magnesium Stearate	4

Examples 22-25

Examples 22-25

The procedure of Example 21 was followed except that the lauryl alcohol was then replaced by, respectively, myristyl alcohol, cetyl alcohol, stearyl alcohol and cetostearyl alcohol.

Exampl 26

Polydextrose (12.6gm) was mixed with molten cetostearyl alcohol (5.4gm). The granules were allowed to cool and sieved through a 20 mesh screen.

Metoclopramide HCl (3.0gm) was dry mixed with the polydextrose/alcohol granules and purified talc (0.21gm). Prior to compression, magnesium stearate (0.21gm) and purified talc (0.21gm) were mixed with the granules. This mixture was then compressed to give 100 tablets each containing,

	mg/Tablet
Metoclopramide HCl	30
Polydextrose	126
Cetostearyl Alcohol	54
Purified Talc	4.2
Magnesium Stearate	2.1

Example 27

The procedure of Example 26 was followed except that the amounts used were chosen such that each tablet contained,

	mg/Tablet
Metoclopramide HCl	30
Polydextrose	210
Cetostearyl Alcohol	90
Purified Talc	6.6
Magnesium Stearate	3.3

Example 28

The procedure of Example 26 was followed except that the amounts used were chosen such that each tablet contained,

	mg/Tablet
Metoclopramide HCl	30
Polydextrose	420
Cetostearyl Alcohol	180
Purified Talc	12.6
Magnesium Stearate	6.3

Example 29

Salbutamol sulphate (0.964gm), equivalent to 0.8gm bas salbutamol was wet granulated with anhydrous lactose (20.8gm), polydextrose (1.25gm) and povidone (0.3gm) and the granules were sieved through a 16 mesh screen. The granules were then dried in a FBD at 60°C.

To the warmed salbutamol containing granules was added molten cetostearyl alcohol (5.5gm). The mixture was allowed to air cool and then passed through a 16 mesh screen.

Talc (0.8gm) and magnesium stearate (0.4gm) were mixed with the granules. The granules were then compressed to give 100 tablets each containing,

Salbutamol Sulphate	9.64
Lactose, anhydrous	208
Polydextrose	12.5
Povidone (K30)	3
Cetostearyl Alcohol	55
Talc	8
Magnesium Stearate	4

The in-vitro dissolution rate of these tablets was measured by the USP Paddle Method at 100rpm in 900ml of aqueous buffer (pH 6.5). Results are given in TABLE 8.

TABLE 8

In Vitro Dissolution of Salbutamol Tablets

Time (Hours)	% (by wt) Released
1	49.5
2	62.4
3	73.2
4	79.1
5	85.5
6	91.0

Example 30

The procedure of Exampl 29 was followed except that the amounts used were chosen such that each tablet contained,

	mg/tablet
Salbutamol Sulphate	9.64
Lactose, anhydrous	190.36
Polydextrose	30
Povidone (K30)	3
Polydextrose	30
Povidone (K30)	3
Cetostearyl Alcohol	55
Talc	8
Magnesium Stearate	4

The in-vitrodissolution of the tablets was measured as described in Example 29. Results are given in TABLE 9.

TABLE 9

In Vitro Dissolution of Salbutamol Tablets

Time (Hours)	% (by wt) Released
1	43.8
2	61.1
3	71.4
4	77.9
5	80.9
6	82.3

Exampl 31

The procedure of Example 29 was followed except that the amounts used were chosen such that each tablet contained,

	mg/Tablet
Salbutamol Sulphate	9.64
Lactose, anhydrous	160.36
Polydextrose	60
Povidone	3
Cetostearyl Alcohol	55
Talc	8
Magnesium Stearate	4

PH 6.5). Results are given in TABLE 10.

TABLE 10
In Vitro Dissolution of Salbutamol Tablets

Time (Hours)	% (by wt) Released
1	41.0
2	57.8
3	68.0
4	74.6
5	81.0
6	83.1

Example 32

Quinidine polygalacturonate (41.25gm), lactose (4.5gm), hydroxypropylmethyl cellulose (1.25gm) and polydextrose (4.5gm) were granulated with water. The granules were sieved through a 16 mesh screen and dried in a fluid bed drier. The granules were mixed with molten cetostearyl alcohol (9.0gm) and allowed to cool. The granules were sieved through a 16 mesh screen and blended with a purified talc (1.0gm). The granules were compressed to give 100 tablets each containing,

	mg/Tablet
Quinidine Polygalacturonate	412.5
Lactose	45
Hydroxypropylmethyl cellulose	12.5
Polydextrose	45
Cetostearyl Alcohol	90
Purified Talc	10

The in-vitrodissolution rate of these tablets was measured by the USP Paddle Method at 100rpm in 900ml of buffer (pH 6.5).

The in-vitro dissolution rate of these tablets was measured by the USP Paddle Method at 100rpm in 900ml of buffer (pH 6.5). Results are given in TABLE 11.

TABLE 11

In Vitro Dissolution of Quinidine Tablets

Time (Hours)	% (by wt) Released
1	15.2
2	26.0
4	41.5
8	60.1
12	72.5
16	79.9
20	89.9

CLINICAL STUDIES

A pharmacokinetic study in 3 healthy volunteers was performed on tablets prepared as described in Example 7. Samples were analysed by enzyme immunoassay. Mean plasma theophylline concentrations are given in TABLE 12.

TABLE 12

Time (Hours)	Mean Plasma Theophylline Concentrations (ug/ml)
0	0.0
1	0.7
2	1.6
3	2.1
4	2.7
7	3.0
8	3.0
10	2.5
12	2.1
24	1.4

It can therefore be seen that the composition of Example 7 exhibits excellent control over the release of theophylline in vivo.

Claims

1. A solid, controlled release, pharmaceutical composition comprising an active ingredient incorporated in matrix comprising a first substance selected from a water soluble polydextrose and a water soluble cyclodextrin and a second substance selected from a C_{12}-C_{36} preferably a C_{14}-C_{22} fatty alcohol, and a polyalkylene glycol, preferably polyethylene glycol.

2. A composition according to claim 1 characterised in that the first substance comprises a cyclodextrin, preferably a beta-cyclodextrin.

3. A composition according to either claim 1 or claim 2 characterised in that the second substance comprises a C_{14}-C_{22} fatty alcohol, preferably stearyl alcohol, myristyl alcohol, cetyl alcohol or cetostearyl alcohol.

4. A composition according to any one of claims 1 to 3 characterised in that the first substance is further selected from a cellulose ether, preferably a hydroxyalkylcellulose or a carboxyalkylcellulose.

5. A composition according to any one of claims 1 to 4 characterised in that the ratio of polydextrose/cyclodectrin/cellulose ether to fatty alcohol/polyalkylene glycol in the composition is between 6 to 1 and 1 to 6, preferably between 4 to 1 and 1 to 4.

6. A composition according to any one of claims 1 to 5 charactiesed in that the composition contains between 1% and 80% (w/w), especially between 1% and 50% (w/w), of the first substance.

7. A composition according to claim 6 characterised in that the composition contains between 2% and 40% (w/w) at the first substance.

8. A composition according to any one of claims 1 to 7 characterised in that the active ingredient comprises a water insoluble drug (as hereinbefore defined).

9. A preparation for us in the production of a solid, controlled release pharmaceutical composition comprising a matrix of a first substance select d from a water soluble polydextrose and a water soluble cyclod xtrin and a second substance selected from a C_{12}-C_{36}, pr ferably a C_{1}-C_{22} , fatty alcohol and a polyalkylene glycol, preferably polyethylene glycol.

10. A preparation according to claim 9 characterised in that the first substance comprises a cyclodextrin, preferably a beta-cyclodextrin, and the second substance comprises a C_{14}-C_{22} fatty alcohol, pref rably stearyl alcohol, myristyl alcohol, cetyl alcohol or cetostearyl alcohol.

Claims for the following Contracting States : AT

1. A process for the preparation of a solid, controlled release, pharmaceutical composition characterised in that mixing an active ingredient with a first substance selected from a water soluble polydextrose and a water soluble cyclodextrin and a second substance selected from a C_{12}-C_{36}, preferably a C_{14}-C_{22} , fatty alcohol and a polyalkylene glycol, preferably polyethylene glycol.

2. A process according to claim 1 characterised in that the first substance comprises a cyclodextrin, preferably a beta-cyclodextrin.

3. A process according to either claim 1 or claim 2 characterised in that the second substance comprises a C_{14}-C_{22} fatty alcohol, preferably stearyl alcohol, myristyl alcohol, cetyl alcohol or cetostearyl alcohol.

4. A process according to any one of claims 1 to 3 characterised in that before, during or after the active ingredient is mixed with the first substance and the second substance, it is also mixed with a cellulose ether, especially a hydroxyalkylcellulose or a carboxylalkycellulose.

5. A process according to any one of claims 1 to 4 characterised in that the ratio of polydextrose/cyclodextrin/cellulose ether to fatty alcohol/polyalkylene glycol in the composition is between 6 to 1 and 1 to 6, preferably between 4 to 1 and 1 to 4.

6. A process according to any one of claims 1 to 5 characterised in that the composition contains between 1% and 80% (w/w), preferably between 1% and 50% (w/w), of the first substance.

7. A process according to any one of claims 1 to 6 characterised in that the active ingredient comprises a water soluble drug (as hereinbefore defined).

8. A process according to any one of claims 1 to 7 for the preparation of a solid, controlled release, pharmaceutical composition, in unit dosage form, for oral admininstration, characterised by granulating an active ingredient with a first substance selected from a water soluble polydextrose and a water soluble cyclodextrin, mixing the granules formed with a second substance selected from a C_{12}-C_{36} fatty alcohol and a polyalkylene gylcol and compressing the granules to give an oral, solid, unit dosage form containing a predetermined, therapeutically active, quantity of the active ingredient.

9. A process according to any one of claims 1 to 7 for the preparation of a solid, controlled release, pharmaceutical composition in the form of a capsules characterised by pelletising, spheronising or granulating an active ingredient with a first substance selected from a water soluble polydextrose and a water soluble cyclodextrin and a second substance selected from a C_{12}-C_{36} fatty alcohol and a polyalkylene glycol to form pellets, spheroids or granules and encapsulating the pellets, spheriods or granules to give a capsule containing a predetermined, therapeutically active, quantity of the active ingredient.

10. A process for the preparation of a matrix for admixture with an active ingredient for form a controlled release pharmaceutical composition characterised by mixing a first substance selected from a water soluble polydextrose and a water soluble cyclodextrin, preferably a beta-cyclodextrin, with a second substance selected from a C_{12}-C_{36}, preferably C_{14}-C_{22}, fatty alcohol and a polyalkylene glycol, preferably polyethylene glycol, to form a controlled release matrix.

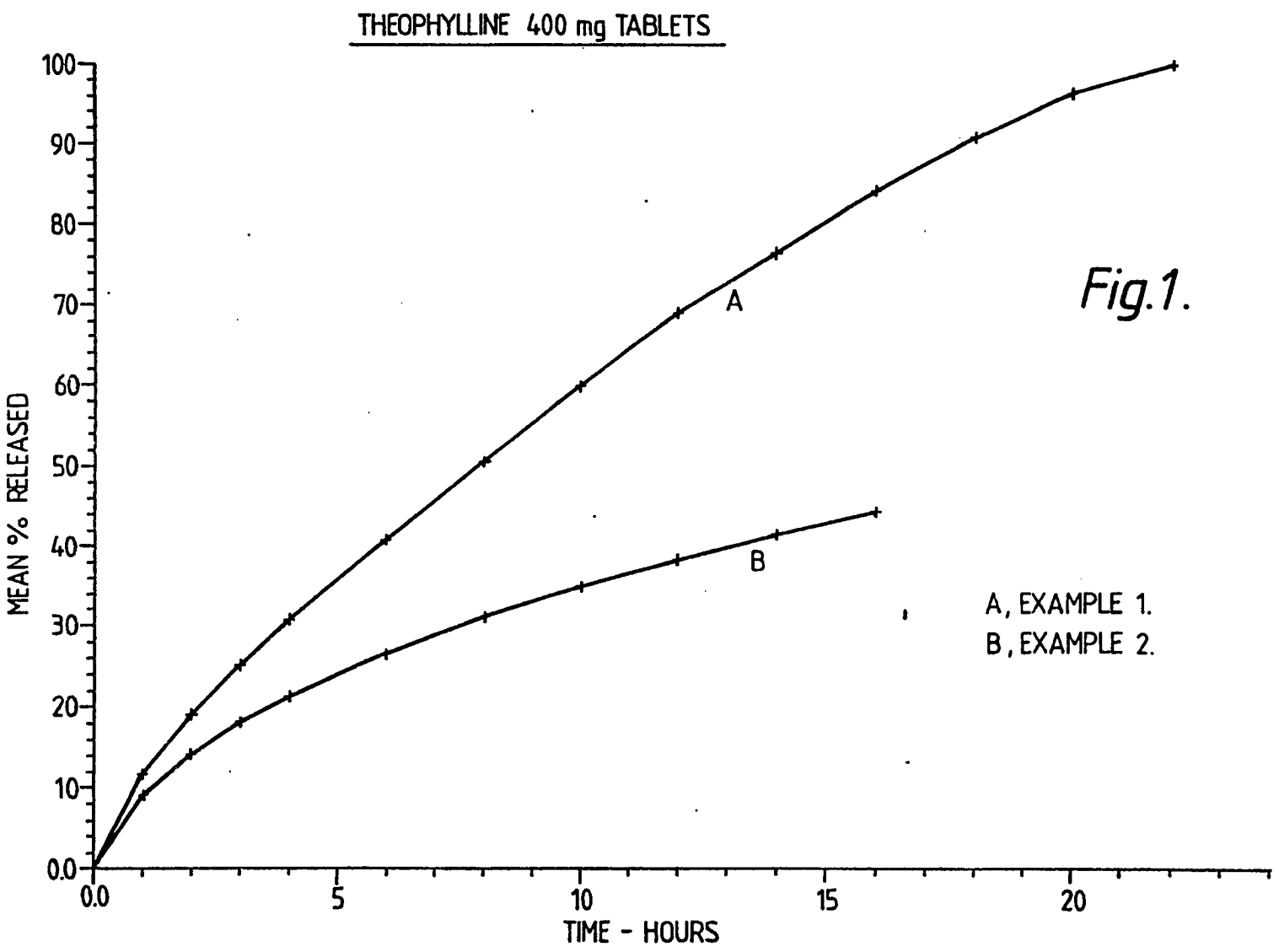

Fig.1.

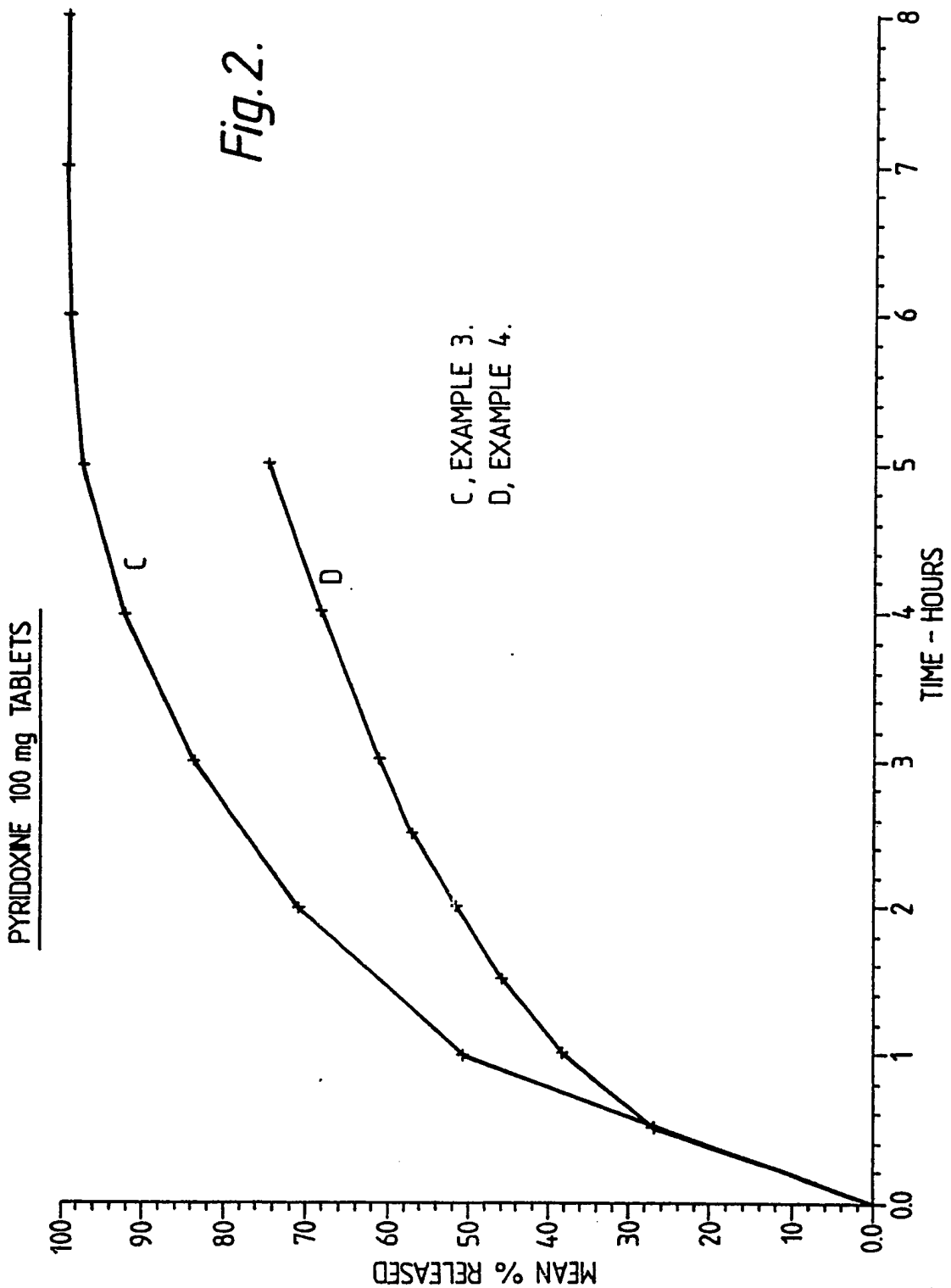
PYRIDOXINE 100 mg TABLETS
MEAN % RELEASED
TIME - HOURS
C
D
C, EXAMPLE 3.
D, EXAMPLE 4.
0.0
10
20
30
40
50
60
70
80
90
100
0.0
1
2
3
4
5
6
7
8

Fig.2.

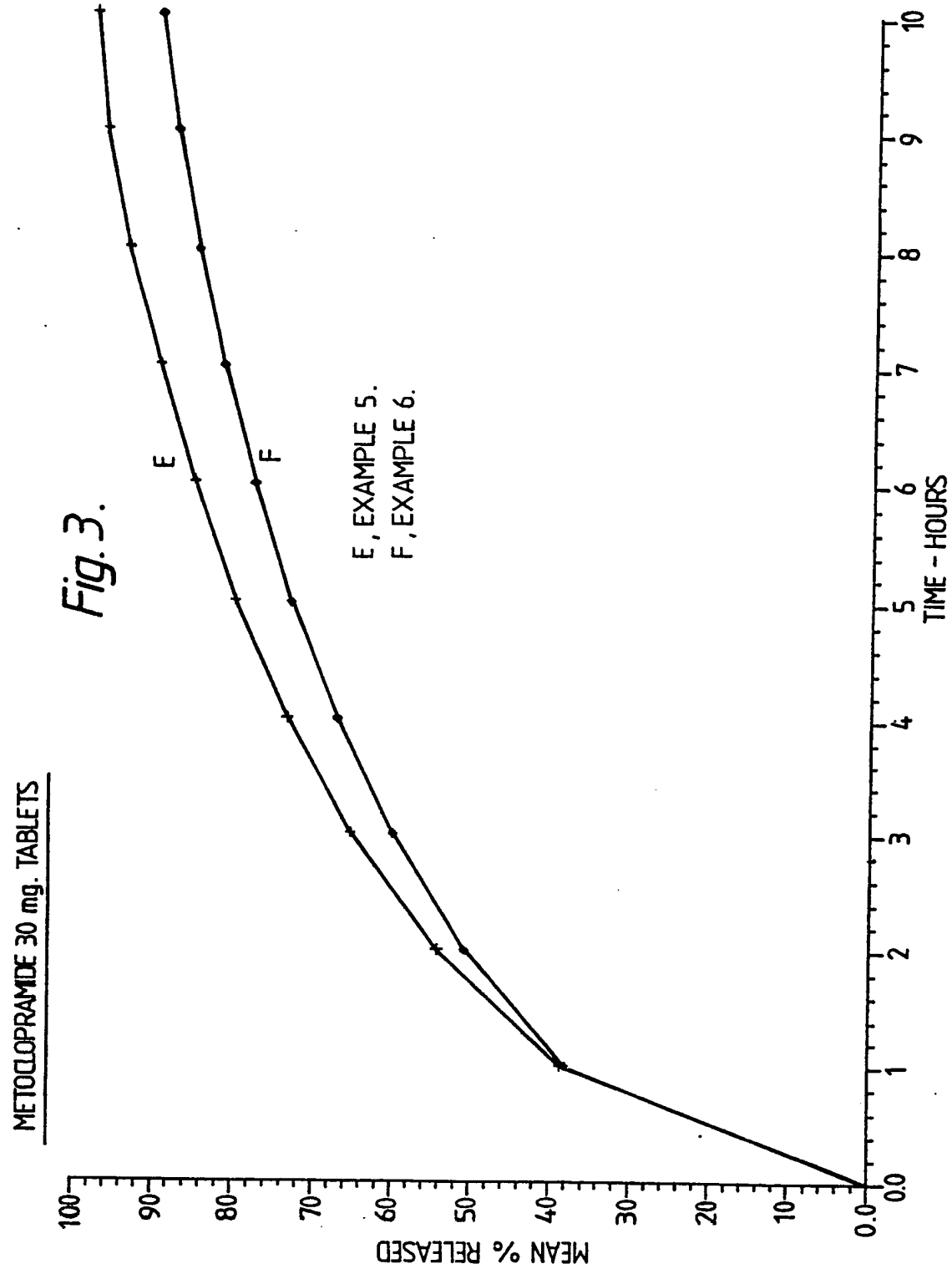
METOCLOPRAMIDE 30 mg. TABLETS
MEAN % RELEASED
TIME - HOURS
E
F
E, EXAMPLE 5.
F, EXAMPLE 6.
0.0
10
20
30
40
50
60
70
80
90
100
1
2
3
4
5
6
7
8
9
10

Fig. 3.